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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

SMITH et al. Atty. Ref.: **2551-49**

Serial No. **09/662,462** Group: **1655**

Filed: **September 15, 2000** Examiner: **Goldberg**

For: **NUCLEIC ACID PROBES AND METHODS FOR DETECTING CLINICALLY IMPORTANT FUNGAL PATHOGENS**

* * * * * * * * * * *

June 24, 2002

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

AMENDMENT UNDER RULE 116

Responsive to the Official Action dated January 24, 2002, entry and consideration of the following amendments and remarks are requested; the period for response having been extended up to and including June 24, 2002, by submission of the requisite petition and fee, attached.

IN THE CLAIMS

Amend the claims as follows.

Cancel claims 12-18, 24-26 and 28-40, without prejudice.

Add the following claims.

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--41. (new) An isolated oligonucleotide molecule consisting of a nucleotide sequence represented by any of SEQ ID NOs: 2 to 13, or 33 to 38, or the RNA

equivalents of said SEQ IDs wherein T is replaced by U, or the complementary nucleic acid of said SEQ IDs, wherein all said oligonucleotide sequences are functional under identical hybridization conditions.

42. (new) An isolated oligonucleotide molecule according to claim 41, for use as a species specific probe in the detection of one of the following fungal pathogens: *Candida albicans, Candida parapsilosis, Candida tropicalis, Candida kefyr, Candida krusei, Candida glabrata,* and *Candida dubliniensis*.

43. (new) Method to detect and identify at least one Candida species in one single assay, including

(i) releasing, isolating and / or concentrating the nucleic acids of the fungal pathogens possibly present in the sample,

(ii) optionally, amplifying the Internal Transcribed Spacer region (ITS) of said nucleic acids with at least one fungal universal primer pair,

(iii) hybridising the nucleic acids of step (i) or (ii) with at least one of the oligonucleotide sequences of claim 41,

(iv) detecting the hybridisation complexes formed in step (iii), and

(v) identifying the Candida species present in said sample, based on the hybridisation complex formed.

44. (new) Method according to claim 43, wherein said fungal universal primer pair is chosen from the following group of primer pairs:

ITS5: GGAAGTAAAAGTCGTAACAAGG (SEQ ID NO:44) and

D1 cont'd

ITS4: TCCTCCGCTTATTGATATGC (SEQ ID NO:45),

ITS5: GGAAGTAAAAGTCGTAACAAGG (SEQ ID NO:44) and

ITS2: GCTGCGTTCTTCATCGATGC (SEQ ID NO:46),

ITS1: TCCGTAGGTGAACCTGCGG (SEQ ID NO:47) and

ITS4: TCCTCCGCTTATTGATATGC (SEQ ID NO:45),

ITS1: TCCGTAGGTGAACCTGCGG (SEQ ID NO:47) and

ITS2: GCTGCGTTCTTCATCGATGC (SEQ ID NO:46),

ITS3: GCATCGATGAAGAACGCAGC (SEQ ID NO:49) and

ITS4: TCCTCCGCTTATTGATATGC (SEQ ID NO:45).

45. (new) Method according to claim 43 wherein wherein the *Candida* species is *Candida albicans* and wherein the at least one probe of step (iii) is

chosen from among SEQ ID NOs:2, 3, 33, 34 and 35.

46. (new) Method according to claim 43 wherein the *Candida* species is *Candida parapsilosis* and wherein the at least one probe of step (iii) is

chosen from among SEQ ID NOs:4 and 5.

47. (new) Method according to claim 43 wherein the *Candida* species is *Candida tropicalis* and wherein the at least one probe of step (iii) is

chosen from among SEQ ID NOs:6 and 36.

48. (new) Method according to claim 43 wherein the *Candida* species is *Candida kefyr* and wherein the at least one probe of step (iii) is

chosen from among SEQ ID NOs:7 and 8.

D1 cont'd

49. (new) Method according to claim 43 wherein the *Candida* species is *Candida krusei* and wherein the at least one probe of step (iii) is

chosen from among SEQ ID NOs:9 and 37.

50. (new) Method according to claim 43 wherein the *Candida* species is *Candida glabrata* and wherein the probe of step (iii) is SEQ ID NO:10.

51. (new) Method according to claim 43 wherein the *Candida* species is *Candida dubliniensis* and wherein the at least one probe of step (iii) is chosen from among SEQ ID NOs:11, 12, 13 and 38.

52. (new) Method according to claim 43 wherein the at least one probe of step (iii) is immobilized to a solid support.

53. (new) Method according to claim 43, further enabling the detection and identification of at least one of the following fungal pathogens: *Aspergillus flavus, Aspergillus versicolor, Aspergillus nidulans, Aspergillus fumigatus, Cryptococcus neoformans* and / or *Pneumocystis carinii*, wherein the nucleic acids of step (i) or (ii) are further hybridized with at least one of the following species specific oligonucleotide probes: SEQ ID NOs: 14 to 32, and 39 to 43.

54. (new) Method for the simultaneous detection and differentiation of at least two Candida species in one single assay, including

(i) releasing, isolating and / or concentrating the nucleic acids of the fungal pathogens possibly present in the sample,

(ii) optionally, amplifying the Internal Transcribed Spacer region (ITS) of said

D1 cont'd

nucleic acids with at least one fungal universal primer pair,

(iii) hybridising the nucleic acids of step (i) or (ii) with at least two of the oligonucleotide sequences of claim 41, under the same hybridization conditions,

(iv) detecting the hybridisation complexes formed in step (iii), and

identifying the Candida species present in said sample, based on the hybridisation complex formed.

55. (new) Method according to claim 54, wherein said fungal universal primer pair is chosen from the following group of primer pairs:

ITS5: GGAAGTAAAAGTCGTAACAAGG (SEQ ID NO:44) and

ITS4: TCCTCCGCTTATTGATATGC (SEQ ID NO:45),

ITS5: GGAAGTAAAAGTCGTAACAAGG (SEQ ID NO:44) and

ITS2: GCTGCGTTCTTCATCGATGC (SEQ ID NO:46),

ITS1: TCCGTAGGTGAACCTGCGG (SEQ ID NO:47) and

ITS4: TCCTCCGCTTATTGATATGC (SEQ ID NO:45),

ITS1: TCCGTAGGTGAACCTGCGG (SEQ ID NO:47) and

ITS2: GCTGCGTTCTTCATCGATGC (SEQ ID NO:48),

ITS3: GCATCGATGAAGAACGCAGC (SEQ ID NO:49) and

ITS4: TCCTCCGCTTATTGATATGC (SEQ ID NO:45).

56. (new) Method according to claim 54 wherein one *Candida* species is *Candida albicans* and wherein at least one of the probes of step (iii) is chosen from among SEQ ID NOs: 2, 3, 33, 34 and 35.

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57. (new) Method according to claim 54 wherein one *Candida* species is *Candida parapsilosis* and wherein at least one of the probes of step (iii) is chosen from among SEQ ID NOs: 4 and 5.

58. (new) Method according to claim 54 wherein one *Candida* species is *Candida tropicalis* and wherein at least one of the probes of step (iii) is chosen from among SEQ ID NOs: 6 and 36.

59. (new) Method according to claim 54 wherein one *Candida* species is *Candida kefyr* and wherein at least one of the probes of step (iii) is chosen from among SEQ ID NOs: 7 and 8.

60. (new) Method according to claim 54 wherein one *Candida* species is *Candida krusei* and wherein at least one of the probes of step (iii) is chosen from among SEQ ID NOs: 9 and 37.

61. (new) Method according to claim 54 wherein one *Candida* species is *Candida glabrata* and wherein one of the probes of step (iii) is SEQ ID NO 10.

62. (new) Method according to claim 54 wherein one *Candida* species is *Candida dubliniensis* and wherein at least one of the probes of step (iii) is chosen from among SEQ ID NOs: 11, 12, 13 and 38.

63. (new) Method according to claim 54 wherein the at least two probes of step (iii) are immobilized to a solid support. --

REMARKS

Reconsideration is requested.

Claims 12-18, 24-26 and 28-40, have been canceled, without prejudice. Claims 41-63 have been added. Support for the amended claims may be found throughout the specification. No new matter has been added. Entry of the above amendments are requested.

The now-canceled claims, as well as the above claims, are not anticipated by the cited art. The Examiner has withdrawn all the previous rejections of the claims under Section 102.

The Examiner admits that Botelho (Yeast, Vol. 10, pg 709-717, 1994) "does not specifically teaches [sic] the exact probes and primers of the instant application." See, pages 3 and 16 of the Office Action dated January 24, 2002 (Paper No. 18).

The Examiner admits that Williams (J. Clinc. Path, vol. 49, No. 1, pgs. M23-M28) "does not specifically teaches [sic] the exact probes and primers of the instant application." See, page 8 of Paper No. 18.

The Examiner admits that "neither Williams-1[1], Linn [J. Clinical Microbiology, Vol. 33, No. 7, pages 1815-1821, July 1995], Messner [Genbank Accession No. UO9325, May 1994] nor Williams-2[2] specifically teaches the exact probes and primers of the instant application." See, page 11 of Paper No. 18.

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[1] Either Williams, J. Clinc. Path, vol. 49, No. 1, pgs. M23-M28 or Genbank Accession No. L47108, September 1995 - the Examiner's remarks are not clear to the undersigned as to which reference is "Williams-1" and clarification is requested in the event the rejection is maintained.

[2] Either Williams, J. Clinc. Path, vol. 49, No. 1, pgs. M23-M28 or Genbank Accession No. L47108, September 1995 - the Examiner's remarks are not clear to the undersigned as to which reference is "Williams-2" and clarification is requested in the event the rejection is maintained.

The Examiner admits that "neither Lott et al [U.S. Patent No. 6,242,178] or [sic] Lott[3] specifically teaches the exact probes and primers of the instant application." See, page 14 of Paper No. 18.

The Examiner admits that none of the above-cited references nor Hogan (U.S. Patent No. 5,595,874) "specifically teach detection of fungal species using a solid support." See, pages 16 and 19 of Paper No. 18.

The Examiner admits that none of the above-cited references nor Hogan (U.S. Patent No. 5,595,874) "specifically teach isolating fungal pathogens from blood." See, page 21 of Paper No. 18.

The Examiner admits that none of the above-cited references nor Hogan (U.S. Patent No. 5,595,874) "specifically teach using homopolymer tail on the oligonucleotides for purpose of detection." See, page 23 of Paper No. 18.

The presently claimed invention provides and claims the following novel nucleic acid sequences and methods which require the use of the following novel nucleic acid sequences:

TGTCACACCAGATTATTACT (SEQ ID NO:2)
TATCAACTTGTCACACCAGA (SEQ ID NO:3)
GTAGGCCTTCTATATGGG (SEQ ID NO:4),
TGCCAGAGATTAAACTCAAC (SEQ ID NO:5),
GGTTATAACTAAACCAAACT (SEQ ID NO:6),
TTTTCCCTATGAACTACTTC (SEQ ID NO:7),
AGAGCTCGTCTCTCCAGT (SEQ ID NO:8),
GGAATATAGCATATAGTCGA (SEQ ID NO:9),
GAGCTCGGAGAGAGACATC (SEQ ID NO:10),

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[3] On page 13 of Paper No. 18 the Examiner refers to "Lott et al" as "Lott" and does not appear to cite a separate "Lott" reference. Clarification is requested in this regard so the applicants may fully respond to any outstanding objection and/or rejection and so that the Board may have a clear record in the event of an appeal. In the event a separate reference "Lott" was intended and not cited to the applicants, a new Office Action is requested, with the date for responding to the same being re-set from the mailing date of the new Action, so that the applicants may fully respond.

TAGTGGTATAAGGCGGAGAT (SEQ ID NO:11),

CTAAGGCGGTCTCTGGC (SEQ ID NO:12),

GTTTTGTTCTGGACAAACTT (SEQ ID NO:13),

TTGTCACACCAGATTATTACTT (SEQ ID NO:33),

GGTTTATCAACTTGTCACACCAGA (SEQ ID NO:34),

GGTATCAACTTGTCACACCAGATT (SEQ ID NO:35),

GGTTATAACTAAACCAAACTTTTT (SEQ ID NO:36),

GGGAATATAGCATATAGTCGA (SEQ ID NO:37),

GGTTTTGTTCTGGACAAACTT (SEQ ID NO:38),

or the RNA equivalents of said probes, wherein T is replaced by U, or the complementary molecules of said probes; or

one of the following novel primer pairs and methods of using the same:

ITS5: GGAAGTAAAAGTCGTAACAAGG (SEQ ID NO:44) and

ITS4: TCCTCCGCTTATTGATATGC (SEQ ID NO:45),

ITS5: GGAAGTAAAAGTCGTAACAAGG (SEQ ID NO:44) and

ITS2: GCTGCGTTCTTCATCGATGC (SEQ ID NO:46),

ITS1: TCCGTAGGTGAACCTGCGG (SEQ ID NO:47) and

ITS4: TCCTCCGCTTATTGATATGC (SEQ ID NO:45),

ITS1: TCCGTAGGTGAACCTGCGG (SEQ ID NO:47) and

ITS2: GCTGCGTTCTTCATCGATGC (SEQ ID NO:46),

ITS3: GCATCGATGAAGAACGCAGC (SEQ ID NO:49) and

ITS4: TCCTCCGCTTATTGATATGC (SEQ ID NO:45).

The Examiner has recognized that these nucleic acid sequences are novel.

The only outstanding rejections of the claims are with regard to obviousness, under 35 U.S.C. § 103. The claims are supported by an enabling disclosure, which provides adequate written support, and the claims are definite.

The Examiner has not cited a reference which teaches or suggests any of the above-noted novel nucleic acid sequences. Rather, the Examiner is understood to

believe that the claimed nucleic acid sequences and methods of using these novel nucleic acid sequences would have been obvious based on teachings in the cited art relating to methods of designing oligonucleotide probes. At best, the Examiner's comments and cited art only provide a basis for a possible suggestion that it may have been obvious to try to make the presently claimed invention. A *prima facie* case of obviousness, under 35 U.S.C. § 103, however requires more than a possible suggestion that it may have been obvious to have tried to make and/or use the presently claimed invention.

The Examiner is urged to appreciate that the claims are not directed to methods of designing oligonucleotide probes, but methods of using specific nucleic acid sequences, which are novel chemical entities, in structural terms, and also a method for detecting *Candida* species using these specific nucleic acids sequences.

A general motivation to search for some probes in a gene does not establish a *prima facie* case of obviousness of the claimed nucleic acid sequences, or methods of using the same, which have been obtained as a result of a specific discovery, such as the applicants' discovery of the presently claimed nucleic acid sequences which are functional under the same hybridisation conditions, for use in detection of *Candida* species. Whether the claimed methods specifically require or state that the same hybridisation conditions may be used is not believed to be critical to the patentability over the cited art as the cited art fails to teach or suggest the specific nucleic acid sequences of the present claims. The previous remarks relating to the same were submitted to stress an unobvious property or advantage of the presently claimed nucleic acid sequences which are inherent to the nucleic acid sequences. While not believed to be necessary, the claims have been amended to recite this characteristic of the claimed products.

The Section 103 rejection of claims 24-26, 28, 30 and 37-38 over Botelho in view of Hogan (U.S. Patent No. 5,595,874) is traversed.

The Section 103 rejection of claims 24-26, 28, 30, 32, 37-38 over Williams et al.

J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) in view of Hogan (US Pat. 5,595,874, January 1997) is traversed.

The Section 103 rejection of claims 24-26, 28-33, 37-38 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin (Genbank Accession Number U10987, March 1996) in view of Hogan (US Pat. 5,595,874, January 1997) is traversed.

The Section 103 rejection of claims 24-26, 28-33, 37-38 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin et al (J. of Clincial Microbiology, Vol. 33, No. 7, pages 1815-1821, July 1995) in view of Hogan (US Pat. 5,595,874, January 1997) is traversed.

The Section 103 rejection of claims 24-26, 28-33, 37-38 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Messner et al (Genbank Accession Number U09325, May 1994) in view of Hogan (US Pat. 5,595,874, January 1997) is traversed.

The Section 103 rejection of claims 24-26, 28-33, 37-38 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Williams et al (Genbank Accession Number L471 08, September 1995) in view of Hogan (US Pat. 5,595,874, January 1997) is traversed.

The Section 103 rejection of claims 24, 34, 37-38 over Lott et al (US Pat. 6,242,178, June 2001) in view of Hogan (US Pat. 5,595,874, January 1997) is traversed.

The Section 103 rejection of claims 35-36 over Botelho et al. (Yeast, Vol. 10, pg. 709-717, 1994) in view of Hogan (US Pat. 5,595,874, January 1997) and Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, pg. 962-967, April 1995) is traversed.

The Section 103 rejection of claims 35-36 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) in view of Hogan (US Pat. 5,595,874, January 1997) and Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, pg. 962-967, April 1995) is traversed.

The Section 103 rejection of claims 24-26, 28-33, 37-38 over Williams et al. J.

Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin (Genbank Accession Number U10987, March 1996) in view of Hogan (US Pat. 5,595,874, January 1997) and Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, pg. 962-967, April 1995) is traversed.

The Section 103 rejection of claims 24-26, 28-33, 37-38 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin et al (J. of Clincial Microbiology, Vol. 33, No. 7, pages 1815-1821, July 1995) in view of Hogan (US Pat. 5,595,874, January 1997) and Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, pg. 962-967, April 1995) is traversed.

The Section 103 rejection of claims 24-26, 28-33, 37-38 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Messner et al (Genbank Accession Number U09325, May 1994) in view of Hogan (US Pat. 5,595,874, January 1997) and Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, pg. 962-967, April 1995) is traversed.

The Section 103 rejection of claims 24-26, 28-33, 37-38 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Williams et al (Genbank Accession Number L471 08, September 1995) in view of Hogan (US Pat. 5,595,874, January 1997) and Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, pg. 962-967, April 1995) is traversed.

The Section 103 rejection of claims 35-36 over Botelho et al. (Yeast, Vol. 10, pg. 709-717, 1994) in view of Hogan (US Pat. 5,595,874, January 1997) and Jordan (US Pat. 6,017,699, January 2000) is traversed.

The Section 103 rejection of claims 35-36 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) in view of Hogan (US Pat. 5,595,874, January 1997) and Jordan (US Pat. 6,017,699, January 2000) is traversed.

The Section 103 rejection of claims 24-26, 28-33, 37-38 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin (Genbank Accession Number U10987, March 1996) in view of Hogan (US Pat. 5,595,874, January 1997) and Jordan (US Pat. 6,017,699, January 2000) is traversed.

The Section 103 rejection of claims 24-26, 28-33, 37-38 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin et al (J. of Clinical Microbiology, Vol. 33, No. 7, pages 1815-1821, July 1995) in view of Hogan (US Pat. 5,595,874, January 1997) and Jordan (US Pat. 6,017,699, January 2000) is traversed.

The Section 103 rejection of claims 24-26, 28-33, 37-38 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Messner et al (Genbank Accession Number U09325, May 1994) in view of Hogan (US Pat. 5,595,874, January 1997) and Jordan (US Pat. 6,017,699, January 2000) is traversed.

The Section 103 rejection of claims 24-26, 28-33, 37-38 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Williams et al (Genbank Accession Number L471 08, September 1995) in view of Hogan (US Pat. 5,595,874, January 1997) and Jordan (US Pat. 6,017,699, January 2000) is traversed.

The Section 103 rejection of claims 35-36 over Lott et al (US Pat. 6,242,178, June 2001) in view of Hogan (US Pat. 5,595,874, January 1997) and Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, pg. 962-967, April 1995) is traversed.

The Section 103 rejection of claims 35-36 over Lott et al (US Pat. 6.242.178, June 2001) in view of Hogan (US Pat. 5,595,874, January 1997) and Jordan (US Pat. 6,017,699, January 2000) is traversed.

The Section 103 rejection of claim 39 over Botelho et al. (Yeast, Vol. 10, pg. 709-71 7, 1994) in view of Hogan (US Pat. 5,595,874, January 1997), Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, page 962-967, April 1995) and Tomblike et al (US Pat. 4,617,102, October 1986) is traversed.

The Section 103 rejection of claim 39 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) in view of Hogan (US Pat. 5,595,874, January 1997), Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, page 962-967, April 1995) and Tomblike et al (US Pat. 4,617,102, October 1986) is traversed.

The Section 103 rejection of claim 39 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin (Genbank Accession Number U10987, March 1996) in

view of Hogan (US Pat. 5,595,874, January 1997), Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, page 962-967, April 1995) and Tomblike et al (US Pat. 4,617,102, October 1986) is traversed.

The Section 103 rejection of claim 39 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin et al (J. of Clinical Microbiology, Vol. 33, No. 7, pages 1815-1821, July 1995) in view of Hogan (US Pat. 5,595,874, January 1997), Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, page 962-967, April 1995) and Tomblike et al (US Pat. 4,617,102, October 1986) is traversed.

The Section 103 rejection of claim 39 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Messner et al (Genbank Accession Number U09325, May 1994) in view of Hogan (US Pat. 5,595,874, January 1997), Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, page 962-967, April 1995) and Tomblike et al (US Pat. 4,617,102, October 1986) is traversed.

The Section 103 rejection of claim 39 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Williams et al (Genbank Accession Number L471 08, September 1995) in view of Hogan (US Pat. 5,595,874, January 1997), Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, page 962-967, April 1995) and Tomblike et al (US Pat. 4,617,102, October 1986) is traversed.

The Section 103 rejection of claim 39 over Lott et al (US Pat. 6,242,178, June 2001) in view of Hogan (US Pat. 5,595,874, January 1997), Fujita et al. (J. of Clinical Microbiology, Vol. 33, No. 4, page 962-967, April 1995) and Tomblike et al (US Pat. 4,617,102, October 1986) is traversed.

The Section 103 rejection of claim 40 over Botelho et al. (Yeast, Vol. 10, pg. 709-717, 1994) in view of Hogan (US Pat. 5,595,874, January 1997) and Shah et al (US Pat. 5,558,989, September 1996) is traversed.

The Section 103 rejection of claim 40 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) in view of Hogan (US Pat. 5,595,874, January 1997) and Shah et al (US Pat. 5,558,989, September 1996) is traversed.

The Section 103 rejection of claim 40 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin (Genbank Accession Number UI 0987, March 1996) in view of Hogan (US Pat. 5,595,874, January 1997) and Shah et al (US Pat. 5,558,989, September 1996) is traversed.

The Section 103 rejection of claim 40 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Lin et al (J. of Clinical Microbiology, Vol. 33, No. 7, pages 1815-1821, July 1995) in view of Hogan (US Pat. 5,595,874, January 1997) and Shah et al (US Pat. 5,558,989, September 1996) is traversed.

The Section 103 rejection of claim 40 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Messner et al (Genbank Accession Number U09325, May 1994) in view of Hogan (US Pat. 5,595,874, January 1997) and Shah et al (US Pat. 5,558,989, September 1996) is traversed.

The Section 103 rejection of claim 40 over Williams et al. J. Clinc. Path. Vol. 49, No. 1, pg. M23-M28) and Williams et al (Genbank Accession Number L47108, September 1995) in view of Hogan (US Pat. 5,595,874, January 1997) and Shah et al (US Pat. 5,558,989, September 1996) is traversed.

The Section 103 rejection of claim 40 over Lott et al (US Pat. 6,242,178, June 2001) in view of Hogan (US Pat. 5,595,874, January 1997) and Shah et al (US Pat. 5,558,989, September 1996) is traversed.

Reconsideration and withdrawal of the above rejections are requested in view of the following distinguishing remarks as well as the remarks of record and the comments above.

The Examiner states that Botelho discloses ITS1 and ITS2 sequences and that probes which were identified unequivocally distinguish between *C. albicans* and other yeast genera as well as between .*C. albicans* and other medically important Candida strains. See, page 3 of Paper No. 18. While the applicants do not agree with the Examiner's assessment of the cited art, the Examiner must also appreciate that Botelho must use **different hybridization conditions** for its probes (see page 714, last

sentence as well as the applicants' Remarks of the Amendment filed January 10, 2002). In fact, the Examiner has not indicated where this advantage of the presently claimed invention is taught or suggested in any of the cited art. Accordingly, the other cited art is similarly deficient in this important aspect of the presently claimed invention. As noted above, the possibility that it may have been obvious to try to make the presently claimed invention does not establish that the presently claimed invention was *prima facie* obvious over the cited art.

The nucleic acid sequences and/or probes disclosed in the cited art have been admitted to be different (i.e., not anticipatory) of the presently recited and disclosed nucleic acid sequences. The Examiner is urged to appreciate that the court has held that some motivation to select the claimed species or subgenus must be taught by the cited prior art, to establish a *prima facie* case of obviousness. See, In re Deuel. 34 USPQ2d 1215 and MPEP § 2144.08 (page 2100-139, August 2001) ("No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared."); In re Baird 29 USPQ2d at 1552; and In re Bell, 26 USPQ2d at 1531 ("Absent anything in the cited prior art suggesting which of the 10^{36} possible sequences suggested by Rinderknecht corresponds to the IGF gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences.").

The Examiner is also urged to appreciate that the court has held that in making an obviousness determination, the PTO should consider the number of variables which must be selected or modified, and the nature and significance of the differences between the prior art and the claimed invention. See, e.g., In re Jones,21 USPQ2d 1941, 1943 (Fed. Cir. 1992) and MPEP § 2144.08, page 2100-140, August 2001. As noted above, the presently claimed invention provides a significant advantage over the cited art in allowing hybridisation under the same conditions.

In an attempt to make up for the deficiency of Botelho, as well as the other cited similar art, the Examiner cites, as a secondary reference, for example, Hogan.

The Examiner alleges that Hogan teaches a method for the selection of specific probes and thus, provides motivation to obtain the probes of the presently claimed nucleic acid sequences. The applicants respectfully submit however that, contrary to the Examiner' s assertions, the teachings of Hogan, and other related secondary references, are generic, and fail to provide any guidance to specifically design the sequences of the presently claimed invention.

The Examiner is urged to review MPEP § 2144.09 (page 2100-148, August 2001), for example, which states as follows:

> "In the biotechnology arts, the existence of a general method of gene cloning in the prior art is not sufficient, without more, to render obvious a particular cDNA molecule. *In re Deuel*, ... 34 USPQ2d 1210, 1215 (Fed. Cir. 1995) ("[T]he existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question of whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs."); *In re Bell*, ... 26 USPQ2d 1529, 1532 (Fed. Cir. 1993)."

The passage in Hogan cited by the Examiner[4] is a general teaching of how to

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[4] "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.

First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10^{0}C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

make a probe which would not have led one of ordinary skill in the art, even in combination with the other cited art, to have made and/or used the specific novel nucleic acid sequences of the presently claimed invention.

The Examiner has not explained how the cited text from Hogan would have actually provided motivation to one of ordinary skill in the art to have specifically identified and selected the specific nucleic acid sequences of the presently claimed invention from a myriad of possible sequences taught by the Examiner's multitude of primary references.

At best, the cited combination of art would have perhaps made it obvious to try to make the presently claimed invention. The Examiner has not established a *prima facie* case of obviousness.

Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be patentable over the cited art and a Notice of Allowance is requested.

Respectfully submitted,

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By: _____

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